IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

PERNIX IRELAND PAIN DAC and PERNIX THERAPEUTICS, LLC,	)	
Plaintiffs,	)	
v.	)	C.A. No. 16-139-WCB
ALVOGEN MALTA OPERATIONS LTD.,	)	
Defendant.	)	

BRIEF IN SUPPORT OF ALVOGEN'S MOTION FOR SUMMARY JUDGMENT OF INVALIDITY UNDER 35 U.S.C. § 101

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Defendant Alvogen Malta Operations Ltd. respectfully requests that the Court enter summary judgment against Plaintiffs Pernix Ireland Pain DAC and Pernix Therapeutics, LLC (collectively, "Pernix") under Rule 56 of the Federal Rules of Civil Procedure that claims 1-4, 11, 12, 17 and 19 of U.S. Patent No. 9,265,760 ("the '760 patent") and claim 1 of U.S. Patent No. 9,339,499 ("the '499 patent") (collectively, "the Asserted Claims") are invalid under 35 U.S.C. § 101.

I. INTRODUCTION

The Asserted Claims are not patent eligible under the Supreme Court's two-part test for patent-eligible subject matter. All of these claims are directed to a law of nature, and none of the claims include an additional inventive concept. Rather, the Asserted Claims "simply state [a] law of nature while adding the words 'apply it.'" Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 72 (2012).

That the Asserted Claims are "directed to" a natural law is expressly admitted in the patent specifications themselves, which state that "the basic concept of the invention" is the similar bioavailability of hydrocodone in patients with and without hepatic impairment ("HI") when administered in an extended-release ("ER") formulation identified as "HC-ER." Crucially, HC-ER is *identical* to a formulation disclosed in a prior art patent application to Devane and that Pernix now markets under the name Zohydro® ER. The inventors merely took the prior art HC-ER formulation from Devane wholesale, and tested it in HI patients. Thus, the natural phenomenon of the human body's metabolism of this prior art formulation is the *only* alleged discovery made by the named inventors. This "discovery" is embodied in "wherein" clauses of the Asserted Claims, which recite standard bioavailability measures (AUC and C_{max})[1] in patients

[1] AUC is an abbreviation for area under the curve and is a measure of the total drug exposure in

with and without mild or moderate HI, as well as a dosage instruction based on these bioavailability measures. These limitations contain the only allegedly inventive concept recited by the Asserted Claims, and formed the sole basis for the Patent Office's erroneous allowance of the Asserted Claims.

Other than the wherein clauses, the Asserted Claims merely recite the conventional and well-known method of treating pain in patients with mild or moderate HI with the known analgesic hydrocodone in an ER oral dosage unit. The named inventors did not add anything inventive to these aspects of the claimed method, either when viewed separately or as a whole. They did not invent hydrocodone. They did not invent extended-release hydrocodone formulations or the hydrocodone-only formulation used to generate the limitations in the wherein clauses – that was taken wholesale from prior art U.S. Patent Appl. Pub. No. 2006/0240105 ("Devane"; Ex. 4). And, of course, they did not invent the treatment of pain in patients with or without HI with such formulations. This was well-understood, routine and conventional activity. Finally, the alleged discovery of the human body's metabolism of Devane's HC-ER formulation was made through routine analysis of bioavailability data generated from a standard HI study required by FDA. Because this "discovery" is no more than an observation and broad application of a natural phenomenon, the Asserted Claims are patent-ineligible as a matter of law.

II. NATURE AND STAGE OF THE PROCEEDINGS

This is a patent action under the Hatch-Waxman Act. On March 4, 2016, Pernix sued Alvogen for infringement of the '760 patent in response to Alvogen's submission of ANDA No.

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the blood plasma over time. (Ex. 1, '760 patent at 11:12-14.) C_{max} is an abbreviation for concentration maximum and connotes the maximum concentration of drug in the blood plasma. (Id. at 11:63-65.)

206986. (D.I. 1, ¶¶ 33-68.) On March 31, 2016, Pernix filed an Amended Complaint, adding the '499 patent to the action. (D.I. 22, ¶¶ 73-83.) On August 3, 2017, the Court issued a Markman order. (D.I. 69.) Fact and expert discovery are now closed, and the Court authorized the filing of this Motion on February 21, 2017. (D.I. 110.)

III. SUMMARY OF THE ARGUMENT

Pernix does not or cannot dispute the following critical facts.

- The Patents-In-Suit state that "[t]he basic concept of the invention" is the similar bioavailability of hydrocodone in patients with and without mild or moderate HI when administered the formulation referred to as HC-ER. (Ex. 1, '760 patent at 15:36-47.)[2]

- The named inventors did not invent HC-ER. Rather, HC-ER is identical to a formulation disclosed in the prior art patent to Devane and which Pernix now markets under the name Zohydro® ER. (Ex. 3, Plaintiff's Responses to RFA Nos. 10, 16-18; Ex. 1, '760 patent at 10:5-6, Examples 6 and 8; Ex. 4, Devane at ¶¶ 99-101.)

- The prior art expressly teaches administering HC-ER, as well as other hydrocodone-only ER oral formulations, to treat pain. (Ex. 4, Devane at ¶ 70; Ex. 5, Huang at 2:21-37, 5:13-17, 7:25-28, Table 14.)

- The prior art expressly teaches administering immediate-release ("IR") and ER hydrocodone combination formulations to treat pain in patients with mild or moderate HI. (Ex. 1, '760 patent at 2:48-56; Ex. 6, Jain at ¶ 64; Ex. 18, Johnson at ACT-HYD2-021165, ACT-HYD2-021170-171; Ex. 19, Smith at PERNIX_HEP0001538, PERNIX_HEP1545-547; Ex. 20, VA Guideline at ACT-HYD2-022220, ACT-HYD2-022277; Ex. 7, Vicodin® Label at ACT-HYD2-022214-215; Ex. 8, Vicoprofen® Label at ACT-HYD2-023201, ACT-HYD2-023203; Ex. 9, Lortab® Label at ACT-HYD2-022210-211.)

The Asserted Claims are "directed" to a natural law because they are entirely premised on the response of the human body to a prior art formulation – the HC-ER formulation disclosed in Devane – and in particular the bioavailability of that formulation in patients without mild or moderate HI. The specifications of the Patents-In-Suit themselves characterize this as the "basic

[2] Exhibit numbers refer to the Appendix of Exhibits in Support of this Motion for Summary Judgment attached to the Declaration of Christopher M. Gallo.

concept of the invention." Further, the Asserted Claims are "conventional" given that the prior art taught methods of treating pain with hydrocodone in patients, including those with HI, and that the Patents-In-Suit utilized the exact same HC-ER formulation as disclosed in Devane. The Asserted Claims fail the patent-eligibility standard as a matter of law.

IV. FACTUAL BACKGROUND

A. Technological Setting of the Patents-In-Suit

1. Hydrocodone Bitartrate and Hydrocodone Dosage Forms

Opioids like hydrocodone are "used clinically primarily for the treatment of pain . . . [and] are amongst the oldest known pharmaceuticals. . . ." (Ex. 1, '760 patent at 1:42-44.) Hydrocodone bitartrate was first approved as an active pharmaceutical ingredient in the United States in 1943. (Ex. 10, Zohydro® ER Label at ALVHYDRO-PTX00013608 ("Initial U.S. Approval: 1943").) At least as early as 2001, various entities began filing patent applications covering hydrocodone ER dosage forms. (See, e.g., Ex. 11, Oshlack; Ex. 12, Devane; Ex. 4, Devane; Ex. 5, Huang.) These dosage forms typically combine immediate with extended-release components using inactive ingredients that were well-known and conventional in the prior art. (See, e.g., Ex. 11, Oshlack at Tables 1A, 2A and 3A; Ex. 4, Devane at Tables 6 and 7; Ex. 5, Huang at Tables 7, 8 and 14.)

The use of such dosage forms to treat pain was also well-known and conventional. For example, each of the patent applications and patents disclosing hydrocodone ER dosage forms also taught methods for using these dosage forms in the treatment of pain. (See., e.g., Ex. 11, Oshlack at 1:15-30; Ex. 4, Devane at ¶ 70; Ex. 5, Huang at 2:21-37, 5:13-17, 7:25-28.)

2. Use of Hydrocodone in the Treatment of Pain Patients Afflicted with HI

Methods for treating pain in HI patients by administering hydrocodone bitartrate in both IR and ER dosage forms were well-known and conventional. For example, the labels for several

existing hydrocodone IR commercial products such as Vicodin® (hydrocodone + acetaminophen), Vicoprofen® (hydrocodone + ibuprofen) and Lortab® (hydrocodone + acetaminophen) note special considerations for administering the products to patients with HI. (Ex. 7, Vicodin® Label at ACT-HYD2-022214; Ex. 8, Vicoprofen® Label at ACT-HYD2-023201, ACT-HYD2-023203; Ex. 9, Lortab® Label at ACT-HYD2-022210-211.) Furthermore, the bioavailability of an ER version of Vicodin® in patients afflicted with HI was known to be similar in patients with and without mild or moderate HI. (Ex. 6, Jain at ¶ 64.) Still further, numerous prior art references discuss the common practice of administering hydrocodone and other opioids for treating pain in patients with HI. (Ex. 18, Johnson at ACT-HYD2-021165, ACT-HYD2-021170-171; Ex. 19, Smith at PERNIX_HEP0001538, PERNIX_HEP1545-547; Ex. 20, VA Guideline at ACT-HYD2-022220, ACT-HYD2-022277.)

B. Development of the Claimed Subject Matter

Development of the claimed subject matter was premised on a prior art hydrocodone ER dosage form. That dosage form, referred to in the Patents-In-Suit as HC-ER, appeared in the above-mentioned Devane (Ex. 4) prior art reference. A company called Zogenix, Inc. obtained the rights to Devane's HC-ER dosage form in 2007 and began efforts to commercialize the formulation. (Ex. 13, Zogenix 30(b)(6) Dep. Tr. at 22:11-23, 24:16-18.) Those efforts culminated in FDA approval of Zohydro® ER, which is identical to Devane's HC-ER in all respects. (Ex. 3, Plaintiff's Responses to RFA Nos. 10, 16-18.)

As part of the approval process, Zogenix followed a FDA Guidance issued in 2003 to conduct an HI study. (Ex. 14, PERNIX_HEP0015644.) As the first named inventor of the Patents-In-Suit explained, "the purpose or point of the FDA Guidance is to standardize how hepatic impairment PK studies are conducted so that everyone conducts the same study of the same study design, and studies conducted on different products can be evaluated in a single

light." (Ex. 15, Hartman Dep. Tr. at 62:20-63:2.)[3]

C. The Patents-In-Suit and Asserted Claims

Based on data generated from the standard HI study, Zogenix filed one of the initial applications leading to the '760 patent on March 13, 2013. This application disclosed using Devane's HC-ER dosage form, referring to it as a "particularly preferred embodiment" and incorporating Devane by reference in its entirety. (Ex. 16, Second Provisional at ¶¶ 68, 100-105.) The initial application also summarized the FDA-mandated clinical study on patients with mild and moderate HI. (Id. at ¶¶ 106-111.) The relevant disclosure appears at Example 8 in the '760 patent, which characterizes the study as a means "to determine the influence of hepatic impairment on the pharmacokinetics and relative bioavailability of hydrocodone and its metabolites." (Ex. 1, '760 patent at 22:50-54.) Example 8 further reports AUC and C_{max} bioavailability measurements from the HI study. (Id. at 23:27-38.) Techniques for measuring AUC and C_{max} were, of course, standard in the art at the time. (Ex. 17, 2003 FDA Guidance at ACT-HYD-023065-068; see also, e.g., Ex. 5, Huang at Table 13 (reporting AUC and C_{max} data for hydrocodone-only ER dosage forms).)

The AUC and C_{max} results demonstrated that the body's physiological response to Devane's HC-ER formulation is similar in patients with no, mild or moderate HI. (Ex. 14, PERNIX_HEP0015629.) This established that the risk of overdose in patients with mild or moderate HI was low and that physicians did not need to adjust the starting dose for these patients. (Id.) They thus summarized the "basic concept" of the alleged invention as follows in the patent specification:

> The ***basic concept of the invention*** can be seen when viewing FIG. 6 and understanding the results shown there. . . . The results show that although there are

[3] Hartman Dep. Tr. refers to the transcript of the deposition of Andrew Hartman, the lead inventor of the Patents-In-Suit.

> some differences in terms of the blood plasma levels obtained, the differences are small and the blood levels are actually very similar pharmacologically. Thus, when using a formulation of the type described here no separate dosing instructions need be given with respect to patients with and without hepatic impairment.

(Ex. 1, '760 patent at 15:36-47.) This "basic concept" formed the basis for the claims of the '760 patent, which include the clause "wherein the starting dose is not adjusted relative to a patient without hepatic impairment." (Ex. 1, '760 patent at claim 1.)

Around the same time as allowance of the '760 patent, the application leading to the '499 patent was filed. (Ex. 2, '499 patent at face page.) The '499 patent is a continuation of the '760 patent and the patents have near-identical specifications. The '499 patent issued on May 17, 2016.

Claim 1 of the '760 patent recites the following:

> 1. A method of treating pain in a patient having mild or moderate hepatic impairment, the method comprising:
> administering to the patient having mild or moderate hepatic impairment a starting dose of an oral dosage unit having hydrocodone bitartrate as the only active ingredient, wherein the dosage unit comprises an extended release formulation of hydrocodone bitartrate, and **wherein the starting dose is not adjusted relative to a patient without hepatic impairment**.

Claim 11 of the '760 patent recites the following:

> 11. The method of claim 9, **wherein the dosage unit provides a release profile of hydrocodone such that the average hydrocodone $AUC_{0\text{-}inf}$ per 20 mg of hydrocodone bitartrate dosed to subjects suffering from moderate hepatic impairment is in the range of about 352 ng*h/mL to about 666 ng*h/mL.**

Claim 1 of the '499 patent recites the following

> 1. A method of treating pain in a patient having mild or moderate hepatic impairment, the method comprising:
> administering to the patient having mild or moderate hepatic impairment an oral dosage unit having hydrocodone bitartrate as the only active ingredient, wherein the dosage unit comprises an extended release formulation of hydrocodone bitartrate,
> **wherein the dosage unit provides a release profile of hydrocodone that:**

> **does not increase average hydrocodone $AUC_{0\text{-}inf}$ in subjects suffering from mild hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 14%; and**
> **does not increase average hydrocodone $AUC_{0\text{-}inf}$ in subjects suffering from moderate hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 30%.**

(Ex. 1, '760 patent at claims 1, 9 and 11; Ex. 2, '499 patent at claim 1.) These three claims are illustrative of the Asserted Claims. Claim 1 of the '760 patent is the only independent claim reciting that the starting dose is not adjusted relative to a patient without HI. All the other Asserted Claims recite that the claimed dosage unit provides certain AUC or C_{max} values in patients with no, mild or moderate HI, either within specific ranges as in claim 11 of the '760 patent or in relative terms as in claim 1 of the '499 patent. All the Asserted Claims recite a method of administering a known dosage form containing a known active to treat a known condition.

V. ARGUMENT

The Asserted Claims are not patent eligible under the Supreme Court's two-part test for patent-eligible subject matter. First, the claims are directed to a natural law because they are entirely premised on the response of the human body to Devane's HC-ER prior art formulation, specifically the bioavailability of that formulation in patients without mild or moderate HI. Second, the other aspects of the claims – the administration of a hydrocodone ER oral dosage unit to treat pain in patients with mild or moderate HI – were routine and conventional and do not add anything inventive to the natural law. Furthermore, the Patents-In-Suit utilized the exact same HC-ER formulation that was disclosed in Devane. The Asserted Claims fail the patent-eligibility standard as a matter of law.

A. Legal Principles

1. Summary Judgment

Under Rule 56(a) of the Federal Rules of Civil Procedure, "[t]he court shall grant summary judgment if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." The moving party bears the burden of demonstrating the absence of a genuine issue of material fact. Matsushita Elec. Indus. Co., Ltd. v. Zenith Radio Corp., 475 U.S. 574, 585-86 (1986). If the moving party has carried its burden, the non-movant must then "come forward with specific facts showing that there is a genuine issue for trial." Id. at 587 (internal quotation marks omitted). Although a court must draw all reasonable inferences in favor of the nonmoving party, a factual dispute is genuine only where "the evidence is such that a reasonable jury could return a verdict for the non-moving party." Id.; Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 278 (1986).

2. Subject-Matter Eligibility

Subject-matter eligibility is a "threshold test," Bilski v. Kappos, 561 U.S. 593, 602 (2010), and a question of law. Intellectual Ventures I LLC v. Capital One Bank (USA), 792 F.3d 1363, 1366 (Fed. Cir. 2015). Summary judgment is thus entirely appropriate where there is no dispute over underlying facts, as is the case here. See, e.g., id. at 1370; Mortgage Grader, Inc. v. First Choice Loan Servs. Inc., 811 F.3d 1314, 1325-26 (Fed. Cir. 2016).

Two Supreme Court decisions set forth the two-step framework for determining whether a claim is patent-eligible under Section 101. Alice Corp. Pty. v. CLS Bank Int'l, 134 S. Ct. 2347, 2355 (2014); Mayo, 566 U.S. at 77-79. The first step is to determine whether the claims are "directed" to a patent-ineligible concept, *i.e.*, a law of nature, abstract idea, etc. Alice, 134 S. Ct. at 2355. If they are, the second step is to "search for an 'inventive concept'—*i.e.*, an element or combination of elements that is 'sufficient to ensure that the patent in practice amounts to

significantly more than a patent upon the [ineligible concept] itself.'" Id. (internal quotation omitted). Merely reciting "steps consisting of well-understood, routine, conventional activity" is "not sufficient to transform unpatentable natural correlations into patentable applications of the regularities." Mayo, 566 U.S. at 80. In other words, "simply appending conventional steps, specified at a high level of generality, to laws of nature . . . cannot make those laws . . . patentable." Id. at 82. Nor can the "inventive concept necessary at step two . . . be furnished by the unpatentable law of nature [] itself." Genetic Techs. Ltd. v. Merial L.L.C., 818 F.3d 1369, 1376 (Fed. Cir. 2016).

In Mayo, the claims recited a two-step method of treatment comprising (1) administering a known drug and (2) determining concentrations of one of its metabolites in the blood, along with two wherein clauses reciting that certain metabolite concentrations indicate a need for dose adjustment. Mayo, 566. U.S. at 74-75. The Supreme Court held these claims directed to a law of nature, inasmuch as the key wherein clauses captured the body's physiological response to administering the known drug in different people. As the Court explained, the claims "set forth laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove effective or cause harm." Id. at 77. In holding the claims invalid as patent ineligible, the Court characterized the peripheral limitations of administering, treating and adjusting as conventional steps that did not transform an un-patentable natural law into patent-eligible subject matter. Id. at 78-80.

Likewise, in Endo Pharm. Inc. v. Actavis Inc., C.A. No. 14-1381, 2015 WL 7253674 (D. Del. Nov. 17, 2015) ("Endo I"), this court held pharmaceutical method of treatment claims invalid as patent ineligible. The Endo claims recited methods for treating pain with the known opioid drug oxymorphone. Endo Pharm. Inc. v. Actavis Inc., C.A. No. 14-1381, 2015 WL

5580488, at *1-2 (D. Del. Sept. 23, 2015) ("Endo II"). Those methods required: (1) providing an oral dosage form; (2) measuring the clearance rate of creatinine, which indicates kidney health; and (3) administering the correct dosage of the drug based on the clearance rate. Id. The claims also recited a wherein clause requiring certain AUC levels in the body after administering the correct dosage. Id. The court characterized the natural law as "the bioavailability of oxymorphone is increased in people with impaired kidney function." Id. at *6. It then rejected Plaintiffs' argument that the method steps did more than simply apply a law of nature as "thoroughly unconvincing" because the subject matter of the alleged invention was merely "'the connection between the severity of renal impairment and the bioavailability of oxymorphone,' or, in other words, the reaction of the human body of a renally impaired individual to oxymorphone, which is unquestionably a natural law." Endo I, 2015 WL 7253674 at *3 (quoting Endo II, 2015 WL 5580488 at *6).

B. The Asserted Claims are Invalid Under Section 101 Because They Are Directed to a Law of Nature and Lack Any Inventive Concept

1. Step One: The Asserted Claims Are Directed to a Law of Nature

Each of the Asserted Claims in this case is directed to a law of nature under step one of the Alice and Mayo framework. The Asserted Claims are premised on the relationship between HI and the bioavailability of hydrocodone in the body after administration of Devane's HC-ER prior art formulation – namely that the response of the human body to this formulation is similar in patients with and without mild or moderate HI. Evaluating the human body's physiological response to a pharmaceutical formulation is a quintessential patent-ineligible law of nature. See, e.g., Mayo, 566 U.S. at 72. Indeed, a law of nature is a relationship that is the consequence of entirely natural processes, even if those natural processes flow from a man-made drug. Endo II, 2015 WL 5580488 at *6 (citing Mayo, 566 U.S. at 77) (finding patient-ineligible claims directed

to administering a certain dosage of the semi-synthetic drug oxymorphone based on measuring the bioavailability of the oxymorphone in patients with renal impairment).

The Patents-In-Suit themselves admit that this natural law is the "basic concept of the invention. . . ." (Ex. 1, '760 patent at 15:36-47; see also Ex. 15, Hartman Dep. Tr. at 142:13-24.) Their specifications expressly state the "basic concept of the invention . . . [is that] differences in terms of the blood plasma levels [between HI and non-HI patients] . . . are small and the blood levels are actually very similar pharmacologically" in response to administering the Devane HC-ER formulation. (Ex. 1, '760 patent at 15:36-44.) Asserted Claim 1 of the '499 patent and Asserted Claims 2-4, 11, 17 and 19 of the '760 patent expressly recite this natural law in their wherein clauses. And Asserted Claim 1 of the '760 patent recites the logical consequence of this natural law – "wherein the starting dose is not adjusted relative to a patient without hepatic impairment." (Ex. 1, '760 patent at claim 1.)[4] As the Endo Court explained, "a patent that . . . describes a relationship that is the consequence of entirely natural processes sets forth a natural law." Endo II, 2015 WL 5580488 at *6 (citing Mayo, 566 U.S. at 77). Or, as Mayo put it, the claim does nothing more than "simply state the law of nature while adding the words 'apply it.'" Mayo, 566 U.S. at 72. There can be no reasonable dispute that the Asserted Claims are directed to a natural law.

2. Step Two: The Asserted Claims Lack Any "Inventive Concept"

The second step of the analysis does not save the Asserted Claims. Excluding the natural law itself, all aspects of the Asserted Claims are routine and conventional, and repeatedly appear in the prior art.

[4] As previously mentioned, the Reasons for Allowance expressly state that the wherein clause requiring non-adjustment of the starting dose was the basis for distinguishing the prior art. (Ex. 21, '760 patent NOA at PERNIX_HEP0000137.)

As an initial matter, to the extent the subject matter of the preamble of the Asserted Claims is limiting, "methods of treating pain in a patient having mild or moderate hepatic impairment" had been routine and common practice for years prior to the Patents-In-Suit. The patent specifications acknowledge that opioids, including hydrocodone, are used primarily to treat pain and are among the oldest known pharmaceuticals. (Ex. 1, '760 patent at 1:42-47.) The specifications also acknowledge that hydrocodone, like other opioids, was routinely administered to patients with HI. (Ex. 1, '760 patent at col. 2:48-4:29.) Indeed, the specifications posit as the problem the alleged invention overcomes that "opioids, including extended release opioids, generally require reduced dosing in patients with hepatic impairment, because the liver is the source of most opioid metabolism." (Id. at 2:41-44.) The specifications further list a number of ER opioids that are used to treat pain in patients with HI. (Id. at 3:10-4:29.) It is thus indisputable that methods of treating pain in patients with HI was well-known, routine and conventional.

With respect to the bodies of the Asserted Claims, the natural law at the heart of the claims is, as discussed above, embodied in the wherein clauses. The remainder of the claims is the step of "administering to the patient having mild or moderate hepatic impairment [a starting dose of][5] an oral dosage unit having hydrocodone bitartrate as the only active ingredient, wherein the dosage unit comprises an extended release formulation of hydrocodone bitartrate. . . ." All aspects of this method step were conventional and routine, whether considered in isolation or in the context of the claims overall, and repeatedly appear in the prior art.

First, the act of "administering" an oral dosage unit merely requires the patient to "deliver[] into the body" the unit, i.e., the same activity required by any patient with respect to

[5] The recitation of "a starting dose" occurs only in Asserted Claims 1-4 of the '760 patent.

any oral dosage form. (D.I. 69 at 1.) Furthermore, the administration of hydrocodone IR and ER products to patients with HI was well-known, conventional and routine. (Ex. 7, Vicodin® Label at ACT-HYD2-022214; Ex. 8, Vicoprofen® Label at ACT-HYD2-023201, ACT-HYD2-023203; Ex. 9, Lortab® Label at ACT-HYD2-022210; Ex. 6, Jain at ¶ 64; Ex. 18, Johnson at ACT-HYD2-021165, ACT-HYD2-021170-171; Ex. 19, Smith at PERNIX_HEP0001538, PERNIX_HEP1545-547; Ex. 20, VA Guideline at ACT-HYD2-022220, ACT-HYD2-022277.) In addition, both Devane and Huang disclosed and taught administering ER dosage forms containing hydrocodone as the only active to treat pain. (Ex. 4, Devane at ¶ 70, claim 81; Ex. 5, Huang at 2:21-37, 5:13-17, 7:25-28, Tables 7, 8 and 14, claim 95.) Moreover, several other opioids were available as single-ingredient ER oral dosage forms. (See Ex. 1, '760 patent at 2:5-12 (listing oxycodone, tapentadol, oxymorphone and morphine as available in such dosage forms).) Thus, administering an ER hydrocodone oral dosage unit to patients with mild or moderate HI was conventional and routine.

Second, it is undisputed that the named inventors did not invent the dosage units described in the claims. On the contrary, they used the exact same "HC-ER" formulation that is disclosed in Devane in the HI study described in the Patents-In-Suit to provide the bioavailability data that is at the heart of the Asserted Claims. (Ex. 3, Plaintiff's Responses to RFA Nos. 10, 16-18.) Plainly, the wholesale re-use of a prior art formulation cannot be the "inventive concept" necessary to render the Asserted Claims patent-eligible subject matter.

In fact, the only aspects of the Asserted Claims that the named inventors even alleged were new are the non-adjustment of the starting dose and the AUC and C_{max} values recited in the wherein clauses. But as discussed earlier, these pharmacokinetic limitations flow directly from the natural law revealed in the routine and FDA-required HI study on the prior art Devane HC-

ER formulation. That is, they flow directly from the response of the human body to Devane's HC-ER formulation in patients with or without mild or moderate HI. It is established law that the "inventive concept necessary at step two [] cannot be furnished by the unpatentable law of nature [] itself." Genetic Techs., 818 F.3d at 1376. Furthermore, the non-adjustment of the starting dose is nothing more than the routine and conventional application of the natural law itself: *because* Devane's HC-ER formulation has similar bioavailability in patients with and without HI, the dosage is not adjusted. As such, these limitations do not save the Asserted Claims.

Finally, if the Asserted Claims were held patentable they would preempt the use of the natural law providing the similar bioavailability of hydrocodone-only ER oral dosage forms in patients with and without mild and moderate HI. The preemptive effect would be broad in scope because the non-adjustment of a starting dose, as recited in claim 1 of the '760 patent, is the *only* medical application of that law. Furthermore, the claimed "oral dosage unit" is primarily defined functionally through the limitations in the wherein clauses, i.e., the natural law and its medical application (no dosage adjustment). The claims have only minimal structural requirements for the oral dosage unit itself, reciting merely that it contain hydrocodone bitartrate as the only active ingredient. Thus, *any* single-ingredient hydrocodone ER oral formulation that meet the limitations in the wherein clauses are preempted by the claims. The named inventors did not provide any inventive concept that could justify this broad preemption of a natural law.

VI. CONCLUSION

For the reasons set forth above, Alvogen respectfully requests that the Court enter summary judgment that claims 1-4, 11, 12, 17 and 19 of the '760 patent and claim 1 of the '499 patent are invalid under 35 U.S.C. § 101.

Respectfully submitted,

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